Vascular endothelial growth factor

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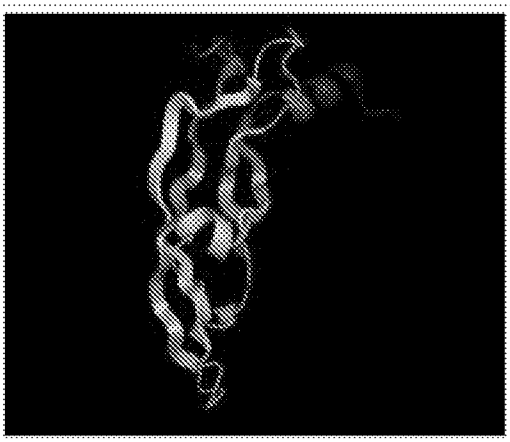
Vascular endothelial growth factor (VEGF) a sub-family of growth factors, more specifically of platelet-derived growth factor family of cystine-knot growth factors. They are important signaling proteins involved in both vasculogenesis (the *de novo* formation of the embryonic circulatory system) and angiogenesis (the growth of blood vessels from pre-existing vasculature).

Contents

Classification

The most important member is VEGF-A. Other members are Placenta growth factor (PlGF), VEGF-B, VEGF-C and VEGF-D. The latter ones were discovered later than VEGF-A, and before their discovery VEGF-A was called just VEGF.

A number of VEGF-related proteins have also been discovered encoded by viruses (VEGF-E) and in the venom of some snakes (VEGF-F).



Crystal structure of Vammin, a VEGF-F from a snake venom

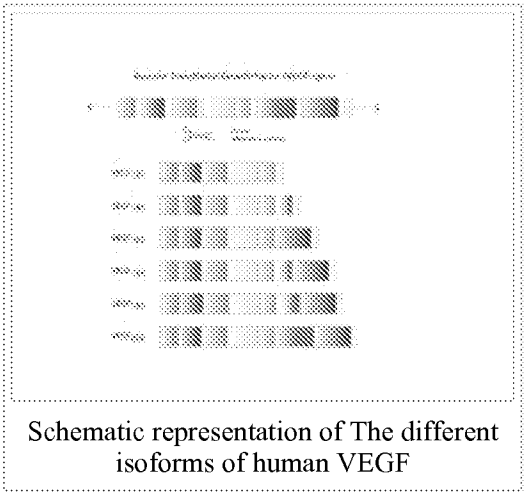
Comparison

Type	Function
VEGF-A	▪ Angiogenesis ▪ ↑ Migration of endothelial cells ▪ ↑ mitosis of endothelial cells ▪ ↑ Methane monooxygenase activity ▪ ↑ αvβ3 activity ▪ creation of blood vessel lumen ▪ creates lumen ▪ creates fenestrations ▪ Chemotactic for macrophages and granulocytes ▪ Vasodilation (indirectly by NO release)
VEGF-B	Embryonic angiogenesis

VEGF-C	Lymphangiogenesis
VEGF-D	Needed for the development of lymphatic vasculature surrounding lung bronchioles
PlGF	Important for Vasculogenesis, Also needed for angiogenesis during ischemia, inflammation, wound healing, and cancer.

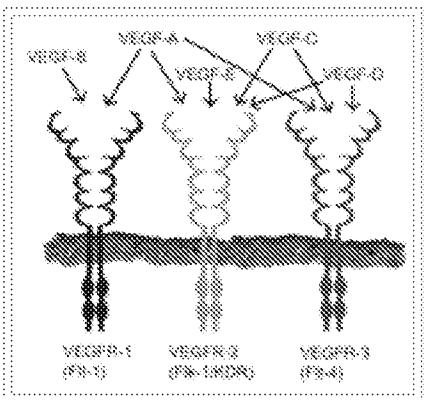
As its name implies, VEGF-A activity has been mostly studied on cells of the vascular endothelium, although it does have effects on a number of other cell types (e.g. stimulation monocyte/macrophage migration, neurons, cancer cells, kidney epithelial cells). *In vitro*, VEGF-A has been shown to stimulate endothelial cell mitogenesis and cell migration. VEGF-A is also a vasodilator and increases microvascular permeability and was originally referred to as vascular permeability factor.

Alternative classification



Schematic representation of The different isoforms of human VEGF

The broad term 'VEGF' covers a number of proteins from two families, that result from alternate splicing of mRNA from a single, 8 exon, *VEGF* gene. The two different families are referred to according to their terminal exon (exon 8) splice site - the proximal splice site (denoted $VEGF_{xxx}$) or distal splice site ($VEGF_{xxx}b$). In addition, alternate splicing of exon 6 and 7 alters their heparin binding affinity, and amino acid number (in humans: $VEGF_{121}$, $VEGF_{121}b$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{165}b$, $VEGF_{189}$, $VEGF_{206}$; the rodent orthologs of these proteins contain one fewer amino acid). These domains have important functional consequences for the VEGF splice variants as the terminal (exon 8) splice site determines whether the proteins are pro-angiogenic (proximal splice site, expressed during angiogenesis) or anti-angiogenic (distal splice site, expressed in normal tissues). In addition inclusion or exclusion of exons 6 and 7 mediate interactions with heparan sulfate proteoglycans (HSPGs) and neuropilin co-receptors on the cell surface, enhancing their ability to bind and activate the VEGF signaling receptors (VEGFRs).



Mechanism

All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation, although to different sites, times and extents. The VEGF receptors have an extracellular portion consisting of 7 immunoglobulin-like domains, a single transmembrane spanning region and an intracellular portion containing a split tyrosine-kinase domain. VEGF-A binds to VEGFR-1 (Flt-1) and VEGFR-2

Types of VEGF and their VEGF receptors.[1]

(KDR/Flk-1). VEGFR-2 appears to mediate almost all of the known cellular responses to VEGF. The function of VEGFR-1 is less well defined, although it is thought to modulate VEGFR-2 signaling. Another function of VEGFR-1 may be to act as a dummy/decoy receptor, sequestering VEGF from VEGFR-2 binding (this appears to be particularly important during vasculogenesis in the embryo). VEGF-C and VEGF-D, but not VEGF-A, are ligands for a third receptor (VEGFR-3), which mediates lymphangiogenesis.

Production

$VEGF_{xxx}$ production can be induced in cells that are not receiving enough oxygen. When a cell is deficient in oxygen, it produces HIF, Hypoxia Inducible Factor, a transcription factor. HIF stimulates the release of $VEGF_{xxx}$, among other functions (including modulation of erythropoeisis). Circulating $VEGF_{xxx}$ then binds to VEGF Receptors on endothelial cells, triggering a Tyrosine Kinase Pathway leading to angiogenesis.

Clinical significance

$VEGF_{xxx}$ has been implicated with poor prognosis in breast cancer. Numerous studies show a decreased overall survival and disease-free survival in those tumors overexpressing VEGF. The overexpression of $VEGF_{xxx}$ may be an early step in the process of metastasis, a step that is involved in the "angiogenic" switch. Although $VEGF_{xxx}$ has been correlated with poor survival, its exact mechanism of action in the progression of tumors remains unclear.

$VEGF_{xxx}$ is also released in rheumatoid arthritis in response to TNF-α, increasing endothelial permeability and swelling and also stimulating angiogenesis (formation of capillaries).

$VEGF_{xxx}$ is also important in diabetic retinopathy (DR). The microcirculatory problems in the retina of people with diabetes can cause retinal ischaemia, which results in the release of $VEGF_{xxx}$, and a switch in the balance of pro-angiogenic $VEGF_{xxx}$ isoforms over the normally expressed $VEGF_{xxx}$b isoforms. $VEGF_{xxx}$ may then cause the creation of new blood vessels in the retina and elsewhere in the eye, heralding changes which may threaten the sight.

$VEGF_{xxx}$ plays a role in the disease pathology of the wet form age-related macular degeneration (AMD), which is the leading cause of blindness for the elderly of the industrialized world. The vascular pathology of AMD shares certain similarities with diabetic retinopathy, although the cause of disease and the typical source of neovascularization differes between the two diseases.

VEGF-D serum levels are significantly elevated in patients with angiosarcoma (PMID 14746640 (http://www.ncbi.nlm.nih.gov/pubmed/14746640))

Once released, $VEGF_{xxx}$ may elicit several responses. It may cause a cell to survive, move, or further differentiate. Hence, VEGF is a potential target for the treatment of cancer. The first anti-VEGF drug, a monoclonal antibody named bevacizumab, was approved in 2004. Approximately 10-15% of patients benefit from bevacizumab therapy, although biomarkers for bevacizumab efficacy are not yet known.

Current studies show that VEGFs are not the only promoters of angiogenesis. In particular FGF2 and HGF [1] (http://www.healthvalue.net/cmettherapies.html) are potent angiogenic factors.

Patients suffering from pulmonary emphysema have been found to have decreased levels of VEGF in the pulmonary arteries.

In the kidney increased expression of $VEGF_{xxx}$ in glomeruli directly causes the glomerular hypertrophy that is associated with proteinuria.[2]

Anti-VEGF therapies

Anti-VEGF therapies [2] (http://www.healthvalue.net/VEGF2engl.html) are important in the treatment of certain cancers and in age-related macular degeneration. They can involve monoclonal antibodies such as bevacizumab (Avastin), antibody derivatives such as ranibizumab (Lucentis), or orally-available small molecules that inhibit the tyrosine kinases stimulated by VEGF: sunitinib (Sutent), sorafenib (Nexavar), axitinib, and pazopanib. Both antibody-based compounds are commercialized. The first two orally available compounds are commercialized, as well. The latter two are in clinical trials, the results of which were presented (June 7) at ASCO.

Bergers and Hanahan concluded in 2008 that anti-VEGF drugs can show therapeutic efficacy in mouse models of cancer and in an increasing number of human cancers. But, "the benefits are at best transitory and are followed by a restoration of tumour growth and progression." [3]

AZ2171, a multi-targeted tyrosine kinase inhibitor has been shown to have antiedema effects by reducing the permeability and aiding in vascular normalization.

External links

- ResearchVEGF.com (http://www.researchvegf.com/)
- MeSH *Vascular+Endothelial+Growth+Factors (http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi?mode=&term=Vascular+Endothelial+Growth+Factors)*
- VEGF antibody (http://www.exactantigen.com/review/vegf.html)

Additionally, VEGF has been show to be associated in the proliferation of inflammatory cytokines in some strains of atopic dermatitis

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